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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,699	02/10/2004	David Bebbington	VPI/00-130-07 DIV US	9174

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EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,699	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 8-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,13,15 and 16* is/are rejected.

7)☒ Claim(s) *8-11 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's amendment of 6-15-06 has been fully considered.

- The deletion of "prodrug" and the definition of L has overcome the previous rejection of 112/2nd paragraph.
- The cancellation of claims 17-34 has also overcome the previous rejections of 112/1st and 2nd paragraphs.
- Thus, previous rejections are now withdrawn.

Claims 2-7 and 17-34 are cancelled.

Claims 1 and 8-16 are pending.

In review the claims, the following new grounds of rejection are presented.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 1, 12, 13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using the compound of formula II wherein R^y does not form a ring (i.e., **pyrimdyl** core), or R^y and R^8 form a benzo ring (i.e., **quinazolinyl** core), does **not reasonably provide enablement** for making and using of the compound of formula II wherein R^y and R^8 form **other heterocyclic** fused rings. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

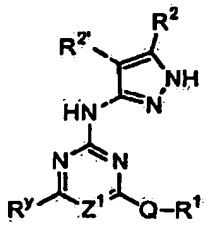
The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 1 and dependents thereon recite:

Claim 1. (Currently amended) A compound of formula II:



II

or a pharmaceutically acceptable salt ~~or prodrug~~ thereof, wherein:

Z^1 is CR^8;

R^y is Z-$R^{3'}$ or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms, or R^y and R^8 are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur;

Q is selected from -N(R^4)-, -O-, –S-, or -CH(R^6)-;

R^1 is T-(Ring D);

Ring D is a 6-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, T-R^3, or V-Z-R^5, and each substitutable ring nitrogen of Ring D is independently substituted by -R^4;

T is a valence bond or a C_{1-4} alkylidene chain, wherein when Q is -CH(R^6)-, a methylene unit of said C_{1-4} alkylidene chain is optionally replaced by -O-, -S-, -N(R^4)-, -CO-, -CONH-, -NHCO-, -SO_2-, -SO_2NH-, -NHSO_2-, -CO_2-, -OC(O)-, -OC(O)NH-, or -NHCO_2-;

Z is a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, -T-W-R^6, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable ring carbon of said fused ring formed by R^2 and $R^{2'}$ is independently substituted by halo, oxo, -CN, -NO_2, -R^7, or -V-R^6, and each substitutable ring nitrogen of said ring formed by R^2 and $R^{2'}$ is independently substituted by R^4;

$R^{3'}$ is selected from -halo, -OR, -C(=O)R, -CO_2R, -COCOR, -$COCH_2$COR, -NO_2, -CN, -S(O)R, -$S(O)_2$R, -SR, -N(R^4)$_2$, -CON(R^7)$_2$, -SO_2N(R^7)$_2$, -OC(=O)R, -N(R^7)COR, -N(R^7)CO_2(C_{1-6} aliphatic), -N(R^4)N(R^4)$_2$, -C=NN(R^4)$_2$, -C=N-OR, -N(R^7)CON(R^7)$_2$, -N(R^7)SO_2N(R^7)$_2$, -N(R^4)SO_2R, -OC(=O)N(R^7)$_2$, or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from –R^7, -COR^7, -CO_2(optionally substituted C_{1-6} aliphatic), -CON(R^7)$_2$, or -SO_2R^7;

each R^5 is independently selected from -R, halo, -OR, -C(=O)R, -CO_2R, -COCOR, -NO_2, -CN, -S(O)R, -SO_2R, -SR, -N(R^4)$_2$, -CON(R^4)$_2$, -SO_2N(R^4)$_2$, -OC(=O)R, -N(R^4)COR, -N(R^4)CO_2(optionally substituted C_{1-6} aliphatic), -N(R^4)N(R^4)$_2$, -C=NN(R^4)$_2$, -C=N-OR, -N(R^4)CON(R^4)$_2$, -N(R^4)SO_2N(R^4)$_2$, -N(R^4)SO_2R, or -OC(=O)N(R^4)$_2$;

V is –O-, -S-, -SO-, -SO_2-, -N(R^5)SO_2-, -SO_2N(R^5)-, -N(R^5)-, -CO-, -CO_2-, -N(R^5)CO-, -N(R^5)C(O)O-, -N(R^5)CON(R^5)-, -N(R^5)SO_2N(R^5)-, -N(R^5)N(R^5)-, -C(O)N(R^5)-, -OC(O)N(R^5)-, -C(R^6)$_2$O-, -C(R^6)$_2$S-, -C(R^6)$_2$SO-, -C(R^6)$_2$$SO_2$-, -C($R^6$)$_2$$SO_2$N($R^5$)-, -C($R^6$)$_2$N($R^5$)-, -C($R^6$)$_2$N($R^5$)C(O)-, -C($R^6$)$_2$N($R^5$)C(O)O-, -C($R^6$)=NN($R^6$)-, -C($R^6$)=N-O-, -C($R^6$)$_2$N($R^5$)N($R^5$)-, -C($R^6$)$_2$N($R^5$)$SO_2$N($R^5$)-, or -C($R^6$)$_2$N($R^5$)CON($R^5$)-;

W is –C(R^6)$_2$O-, -C(R^6)$_2$S-, -C(R^6)$_2$SO-, -C(R^6)$_2$$SO_2$-, -C($R^6$)$_2$$SO_2$N($R^5$)-, -C($R^6$)$_2$N($R^5$)-, -CO-, -$CO_2$-, -C($R^6$)OC(O)-, -C($R^6$)OC(O)N($R^5$)-, -C($R^6$)$_2$N($R^5$)CO-, -C($R^6$)$_2$N($R^6$)C(O)O-, -C($R^6$)=NN($R^6$)-, -C($R^6$)=N-O-, -C($R^6$)$_2$N($R^6$)N($R^6$)-, -C($R^6$)$_2$N($R^6$)$SO_2$N($R^6$)-, -C($R^6$)$_2$N($R^6$)CON($R^6$)-, or -CON($R^6$)-;

each R^6 is independently selected from hydrogen or an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring; and

R^8 is selected from -R, halo, -OR, -C(=O)R, -CO_2R, -COCOR, -NO_2, -CN, -S(O)R, -SO_2R, -SR, -N(R^4)$_2$, -CON(R^4)$_2$, -SO_2N(R^4)$_2$, -OC(=O)R, -N(R^4)COR, -N(R^4)CO_2(optionally substituted C_{1-6} aliphatic), -N(R^4)N(R^4)$_2$, -C=NN(R^4)$_2$, -C=N-OR, -N(R^4)CON(R^4)$_2$, -N(R^4)SO_2N(R^4)$_2$, -N(R^4)SO_2R, or -OC(=O)N(R^4)$_2$; provided that when Q is -NH- and $R^{3'}$ and R^8 are taken together, R^1 is other than pyrazol-3-yl or a bicyclic ring system containing said pyrazol-3-yl ring.

Note, the limitation of "R^y and R^8 are taken together to form a fused, optionally substituted 5-7 membered, unsaturated or partially unsaturated, ring having 0-3 heteroatoms selected from nitrogen, oxygen, or sulfur" encompasses fused rings of various sizes and multiple heteroatoms besides **quinazoline**. Therefore, formula II has a variable core covers pyrimidine, quinazoline as well as all other heterocylic bicycles (e.g., pyrido-pyrimidine, pyrimido-pyrimidine, pyrazo-pyrimdine, thieno-pyrimidine, oxazo-pyrimidine, etc.). Thus, the scope of claim 1 and its dependent claims that includes the fused ring formed by R^y and R^8 is unduly broad.

The amount of direction or guidance presented: Regarding the preparation of compounds of formula II, the specification only provides the starting material for **pyrimidinyl**, and **quinazolinyl** cores. Note, the generic reaction Schemes I and II do not appear to teach a reaction step of R^y and R^8 forming a ring. Species made are those of **pyrimidinyl**, and **quinazolinyl** cores, and not other bicyclic heterocyclic cores. The specification is silent as to the availability of necessary reactants needed to prepare a compound of formula II with other fused heterocyclic cores outside of working examples. Note, **In re Howarth** 210 USPQ 689; **Ex parte Moersch** 104 USPQ 122, for the need to show starting material sources commensurate with the claims' scope.

Regarding the biological activity, the specification only details various bioassay methods without indicating which compounds have been tested. Assuming all compounds in the working examples have been tested, their activity cannot be extrapolated to other compounds of formula

II with a core of other than **pyrimidinyl** and **quinazolinyl** as there is no evidence of recognized biological equivalency for such diverse groups.

Thus, the specification does not provide sufficient enablement commensurate with the broad Markush group of formula II.

The state of the prior art: Typically, pyrimidinyl compounds are known to treat cancer as evident by **Bradbury et. al.** (US'326 B1). Bradbury's formula I; however, allows for *pyrazolyl-amino* at the 2nd position, does not allow for any fused rings. Thus, the state of the prior art does not provide adequate enablement for making compounds in commensurate with the scope of formula II and use them accordingly.

The relative skill of those in the art: Even with the advanced training, the skilled medicinal chemist and/or clinician would have to carry out extensive research to make a myriad number of compounds, and select an effective compound from such a large Markush group for the treatment of cancer or tumor. Given a large Markush group of the claimed formula II, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification does not provide starting materials for making compounds of formula II with various heterocyclic ring and complicated substituents. It also fails to provide biological data for using the claimed compounds. Thus, with the large Markush group of formula II, without the guidance for starting material sources of various bicyclic heterocyclic

cores, undue experimentation is necessary for making such an array of compounds as well as establishing biological activity for those compounds.

Claim Objections

2. Claims 8-11 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Reference cited on PTO-892

3. The reference of **Bradbury et. al.** (US'326) is cited as the closest prior art. While it teaches compounds of pyrimidine with substituents at the 2- and 4-position with Q_1 could be a pyrazole, it fails to teach or fairly suggest a modified pyrimidyl compound with a substituent at the 6-position that is equivalent to the instant R^y.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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10-12-06

Tamthom N. Truong
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